AMENDMENT TRANSMITTAL LETTER (Large Entity) Applicant(s): **Weichao G. Chen et al.**					Docket No. **16575(PC10866A)**
Application No. **09/836,035**	Filing Date **April 17, 2001**	Examiner **E. Huang**	Customer No. **23389**	Group Art Unit **1625**	Confirmation No. **8768**

Invention: **SODIUM-HYDROGEN EXCHANGER TYPE 1 INHIBITOR**

COMMISSIONER FOR PATENTS:

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST # PREV. PAID FOR		NUMBER EXTRA CLAIMS PRESENT	RATE	ADDITIONAL FEE
TOTAL CLAIMS	30	-	31	=	0	x $18.00	$0.00
INDEP. CLAIMS	3	-	4	=	0	x $86.00	$0.00
Multiple Dependent Claims (check if applicable) ☐							$0.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT							$0.00

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Signature

Dated: **September 9, 2004**

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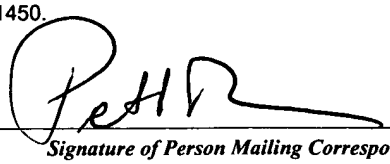

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RESPONSE UNDER 37 C.F.R. §1.116 EXPEDITED PROCEDURE EXAMINING GROUP 1625

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Weichao G. Chen et al.

Examiner: Evelyn Huang

Serial No: 09/836,035

Art Unit: 1625

Filed: April 17, 2001

Docket: 16575 (PC10866A)

For: SODIUM-HYDROGEN EXCHANGER TYPE 1 INHIBITOR

Dated: September 9, 2004

Confirmation No.: 8768

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

RESPONSE UNDER 37 C.F.R. §1.116

Sir:

This is in response to the outstanding Official Action dated June 9, 2004.

All the claims submitted for examination in this application have been rejected on substantive grounds. Applicants have considered the grounds of rejection imposed in the

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Dated: September 9, 2004

Peter I. Bernstein

outstanding Official Action and respectfully submit that all the claims currently in this application are patentable thereover.

Four substantive grounds of rejection have been imposed in the outstanding Official Action. The first of these substantive grounds is directed to Claims 1-29. These claims stand rejected, under 35 U.S.C. §102(a), as being anticipated by International Publication No. WO 99/43663 to Hamanaka et al.

The Official Action avers that inherent anticipation is present in view of the disclosure in Hamanaka et al. of a compound which metabolizes to [5-cyclopropyl-1-(2-quinolon-5-yl)-1H-pyrazole-4-carbonyl]guanidine. Specifically, the Official Action states that Hamanaka et al. discloses the prior art compound [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]quanidine. This compound is metabolized, by hydroxylation, to the compound recited in Claim 2, which is a compound within the scope of generic Formula I of Claim 1.

Applicants respectfully submit that this ground of rejection is unavailing. This is so insofar as the proviso of Claim 1 excludes the compound, [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine from the class of prodrugs from which the generic compound of formula I may be metabolized.

The outstanding Official Action does not appreciate that Claim 1 specifically excludes the aforementioned compound not from the scope of compounds having the structural formula I but rather from the class of prodrugs that are metabolized to a compound within the contemplation of the compound having the structural formula I.

It is axiomatic that the applicant is his own lexicographer. Negative limitations, of the type set forth in Claim 1, are deemed definite. In re Schechter, 205 F.2d 185, 98 USPQ 144

(CCPA 1953); In re Duva, 387 F.2d 402, 156 USPQ 90 (CCPA 1967). Applicants have availed themselves of the right to exclude [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine from the class of prodrugs that produce compounds having the formula I in Claim 1. Since that compound is the only prior art compound disclosed in Hamanaka et al. that metabolizes to the compound of formula I, that reference does not anticipate any of Claims 1 to 29.

The second substantive ground of rejection is directed to Claims 1-29 and 31. These claims stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Hamanaka et al.

The predicate for this ground of rejection is the generic disclosure in Hamanaka et al. of a pyrazole-carbonyl guanidine compound for treating ischemia. The Official Action submits that the specific compound [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine is set forth as one of two compounds in Claim 103 of the Hamanaka et al. reference. The Official Action argues that this compound differs from the aforementioned compound of Claim 103 of Hamanaka et al. by the inclusion of an additional 2-hydroxy group on the quinolinyl moiety. The Official Action avers that 2-hydroxy is an optional substituent among a small genus, citing Claim 102, which provides a definition of R^2.

That this is a small group is indeed stretching the word "small." In Claim 102 R^2 defined as a quinolinyl, an isoquinolinyl, an indazolyl or a benzimidazolyl ring. This ring may be substituted with one or two substituents. One of the substituents is indeed hydroxy. However R^2 may be, in addition, halo, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkyl, (C_1-C_4)alkanoylamino, (C_1-C_4)alkoxycarbonylamino, sulfonamino, (C_1-C_4)alkylsulfonamido, mono-N- or di-N, N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-(C_1-C_4)alkylcarbamoyl, (C_1-C_4)alkysulfonyl or mono-N- or di-N, N-(C_1-C_4)alkylaminosulfonyl. In addition, if the

substituents are (C_1-C_4)alkoxy or (C_1-C_4)alkyl, these substituents themselves may be optionally monosubstituted with hydroxy, (C_1-C_4)alkanoylamino, (C_1-C_4)alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, (C_1-C_4)alkylsulfonyl or mono-N- or di-N,N-(C_1-C_4)alkylaminosulfonyl or optionally substituted with 1 to 5 fluorines.

To suggest that this class of compounds, which probably number in the hundreds of possibilities, make obvious the single compound recited in Hamanaka et al. is thus unreasonable. To further state that the monosubstitution on a quinolinyl ring of hydroxy, on the 2-position, which must then be tautomerized to 2-oxo, is nothing more than the appropriation of applicants' invention wherein the present application is used as a template to find prior art which reads on its disclosure. In re Rouffet, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Obviousness may not be established using hindsight or the teachings or suggestions of the inventor. Para-Ordnance Manufacturing Inc. v. SGS Importers International Inc. 73 F.3d 1085, 1087, 37 USPQ2d 1237, 1239 (Fed. Cir. 1995), cert. denied, 519 U.S. 822 (1996).

To summarize the above remarks, applicants submit that Hamanaka et al. does not, by its teaching of a generic formula which does not encompass the claims of the present application, so much as create a presumption of obviousness of the rejected claims. However, in a surfeit of caution, applicants have presented a showing, the Allen Declaration, discussed in the previous response, which rebuts any presumption of obviousness albeit the above remarks establish that no presumption of obviousness is presented in the present application.

The showing presented in the Declaration, evidencing longer plasma half-life of the claimed compound over the precursor compound, is dismissed in the outstanding Official Action as not being commensurate in scope to the scope of the claims.

If ever there was a showing of an unexpected result, applicants submit that it is been done in the Allen Declaration of record. To dismiss this showing by arguing that claimed compound is a prodrug of the prior art compound and thus one skilled in the art would expect the precursor compound to have a shorter plasma half-life is not understood.

Simply stated, applicants have presented a showing establishing unexpected results. This showing is dismissed out of hand in the outstanding Official Action based on a mere statement, supported by no data or any technical authority to sustain its conclusion. That a compound similar in structure to a prior art compound produces a longer acting therapeutic effect is indeed unexpected. Attention is directed to MPEP §716.02(a)(II) which includes a Board of Patent Appeals and Interferences decision that stands for the proposition that superior therapeutic activity of a claimed compound represents an unexpected result. Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).

The third ground of rejection is directed, again, to Claims 1-29 and 31. These claims stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Hamanaka et al. in view of Principles of Pharmacology, Basic Concepts & Clinical Applications (1995), edited by Munson et al. and Beedham et al., Drug Metabolism and Disposition, 20(6), 889-895 (November-December 1992).

The Official Action argues that Munson et al. discloses that hydroxylation reactions are well known in the pharmaceutical arts as a Phase I metabolitic transformation of drugs. The oxidation of quinoline to 2-quinolone by an oxidase from the liver is described in the

Beedham et al. abstract. Thus, the prior art quinoline compound is a prodrug of the instant quinoline compound and is expected to share similar biological activities.

As applicants have argued twice in the past, Munson et al. teaches that metabolism may occur under Phase I or Phase II metabolic transformation and, moreover, there are multiple types of Phase I transformations. The teaching of Munson et al., as summarized in applicants' earlier response, is that the likelihood of metabolism, the type of metabolism, the extent of metabolism and the position of metabolism in a molecule cannot be predicted without extensive experimentation.

As far as Beedham et al. is concerned, that reference discloses oxidation at the 2-position of a quinoline ring. However, as discussed in applicants' previous responses, the compounds disclosed therein are dissimilar to applicants' claimed compounds. As stated above, Munson et al. teaches that there are a wide variety of mechanisms involved in a metabolic reaction. Moreover, a wide variety of substrates are vulnerable to transformation. As such, while the instant invention and Beedham et al. share a quinolone moiety in their respective compounds, other groups on the respective compounds may be metabolized instead of, or in addition to, the group in question to provide very different compounds.

The above remarks make it apparent that the Official Action combination of Hamanaka et al., Munson et al. and Beedham et al. is not motivated by the teachings of these prior art references. Rather, it is apparent that the combination of the applied references is prompted by a reading of the specification of the present application. Such motivation is improper and fails to present a prima facie case of obviousness. In re Rouffet, ibid.

The fourth final substantive ground of rejection is directed to all the claims currently in this application, Claims 1-29 and 31. Claims 1-29 and 31 stand rejected, under the

judicially created doctrine of obviousness-type double patenting, over Claims 52 and 124 to 128 of U.S. Patent 6,492,401 to Hamanaka et al.

The applied claims of the '401 Hamanaka at al. patent is predicated on the disclosure therein of the compound [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine, as disclosed in Claim 52, and the use of this compound in reducing tissue damage, as set forth in Claims 124 to 128. As in the previous three grounds of rejection, applicants respectfully traverse this fourth substantive ground of rejection.

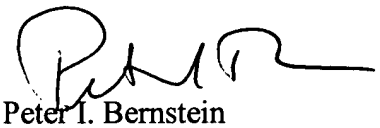
The above remarks establishing (1) that a prima facie case is not made out by Hamanaka et al., equivalent to the '401 patent, and that, even if it were, the showing presented in the Allen Declaration rebuts that presumption of obviousness is reiterated and reemphasized. That is, applicants submit that the earlier remarks, establishing patentability over the rejection of Claims 1-29 and 31 under 35 U.S.C. §103(a) over Hamanaka et al., establish patentablity over this fourth ground of rejection.

Reconsideration and removal of the four substantive grounds of rejection in view of the above remarks is deemed appropriate. Such action is respectfully urged.

The above remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and passage to issue of these claims, Claims 1-29 and 31, is

therefore respectfully solicited.

Respectfully submitted,



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